REMARKS

Applicants' attorney wishes to thank the Examiner for the careful consideration given to this case. Claims 32-59 and 75-87 are pending in this application. No claim amendments are submitted at this time.

35 U.S.C. § 112, first paragraph- "Enablement"

The Examiner has maintained the rejection of claims 32-59 and 75-87 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner has taken the position that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to make or use the claimed invention. Specifically, while the Examiner appears to concede that the specification as filed would enable a person skilled in the art to make and use the invention *in vitro*, the Examiner contends that "undue experimentation" would be required of one of ordinary skill in the art to make and use the invention *in vivo*. The Examiner appears to have based this rejection on the belief that the *in vitro* examples provided in the specification do not correlate to *in vivo* use of the method of the invention. Applicants respectfully disagree.

Applicants' *in vitro* data clearly show that expression of human ICAM in cultured HEK (*H*uman *E*mbryonic *K*idney) cells can be inhibited using Applicants' siRNA. However, the Examiner appears to contend that Applicants' cultured HEK cells are not an art-recognized correlative model for human cells. First and foremost, one of ordinary skill in the art would recognize cultured HEK cells as being a correlative model for human cells because HEK cells *are* human cells. Additionally, Applicants assert that because HEK cells are derived from human cells, HEK cells express human ICAM, and the silenced ICAM gene is of the same sequence and performs the same function in cultured HEK cells as in *in vivo* human cells. Thus, the skilled artisan would reasonably expect that the inhibition of human ICAM induced by Applicants'

siRNA shown in HEK cells would correlate to inhibition of expression of human ICAM in any human cell.

The Examiner further asserts that, at the time of the invention, cell culture results were not readily extrapolated to *in vivo* applications and recalls the teachings of Lu et al., Samarsky et al., and Downward et al. as providing evidence to such effect. In fact, Lu et al., Samarsky et al., and Downward et al. each appear to suggest that provided the siRNA reached the target cell, *in vitro* data correlate well to *in vivo* applications, and each references cited by the Examiner asserts that siRNA holds great therapeutic promise clearly acknowledging that successful use of siRNA *in vitro* correlates to successful use of siRNA *in vivo*. Moreover, at the time of the invention, numerous examples were available that showed *in vivo* silencing of genes using siRNA in various model systems including, for example, *C. elegans*, *D. melanogaster*, mice, etc., and experimental data showed that an siRNA developed using cultured cells *in vitro* could be used to target the same gene *in vivo*. For example, Xia et al., "siRNA-mediated gene silencing in vitro and in vivo", *Nature Biotechnology*, 20: 1006-1010 (2002) shows viral-mediated expression of siRNA inhibits expression of eGFP and endogenously expressed β-glucuronidase in mice *in vivo*; McCaffery et al. "RNA Interference in Adult Mice," *Nature*, 418: 38-39 (2002) shows *in vivo* delivery of naked siRNAs to livers of adult mice using a modified hydrodynamic transfection method, which inhibits expression of firefly luciferase and hepatitis C viral proteins in the livers of adult mice; and Filleur et al. "siRNA-Mediated Inhibition of Vascular Endothelial Growth Factor Severely Limits Tumor Resistance to Antiangiogenic Thrombospondin-1 and Slows Tumor Vascularization and Growth," *Cancer Research*, 63: 3919-3922 (2003) shows an siRNA targeting VEGF developed *in vitro* using cultured cells, which inhibits VEGF expression in grafted tumor cells when the VEGF siRNA is delivered

systemically by i.p. injection (each of these references are attached hereto for the Examiner's convenience). These references clearly show the effective use of siRNA *in vivo* through at least three (3) different mechanisms, and that siRNA developed *in vitro* correlate to *in vivo* applications. Therefore, one of ordinary skill in the art would reasonably expect siRNA shown to successfully inhibit expression of human ICAM in cultured HEK cells *in vitro* would inhibit expression of human ICAM *in vivo* and the observed *in vitro* effect of administration of Applicants' siRNA does correlate with *in vivo* applications.

The Examiner appears to imply that the teaching of Lu et al., Samarsky et al., and Downward et al. suggest that delivery of siRNA may be a limiting factor for therapeutic use of siRNA. Applicants respectfully assert that following development of Applicants' siRNA and based upon the guidance provided in Applicants' specification only routine experimentation would be necessary deliver the siRNA. There are numerous formulations, routes of administration, etc. known in the art, and it is well within the purview of one or ordinary skill in the art to determine which mode of delivery, formulation, dosage, etc. is appropriate for a specific therapeutic use. In fact, Applicants' specification provides specific guidance as to various formulations and dosage determination. Therefore, given the knowledge that Applicants' siRNA inhibits expression of human ICAM, the skilled artisan would be enabled to determine an appropriate means for delivering Applicants' siRNA based on Applicants' specification.

With regard to independent claim 75, aberrant expression of human ICAM is known to be associated with complications due to Type I Diabetes. Therefore, based on Applicants' exemplary *in vitro* data, one of ordinary skill in the art would reasonably expect that

contacting cells in a patient that are aberrantly expressing human ICAM due to Type I Diabetes would effectively treat that patient.

Applicants clearly show that the claimed siRNA effectively inhibits ICAM expression and that this inhibition correlates with *in vivo* applications. Moreover, Applicants' specification provides enabling disclosure for a vast number of formulations and routes of administration. Using Applicants' siRNA, one of ordinary skill guided by the specification as filed could effectively use Applicants' claimed method. Therefore, the specification as originally filed is enabling and the Examiner's rejection should be withdrawn. Reconsideration is respectfully requested.

CONCLUSION

In the event that an additional fee is required for this Response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicants' attorney, she is invited to contact the undersigned at her convenience.

Respectfully submitted,

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